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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,448	07/21/2000	MICHAEL R. O'DONOHUE	1533.1010002/SRL/CMb	4431

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 11/19/2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/621,448	O'DONOHUE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-8 and 18-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-8 and 18-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Application Status***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/04/02 has been entered.

Claims 1, 6-8, and 18-21 are pending in the application.

Amendment to claims 7, 18, 19, 20, and 21 in Paper No. 18, filed 10/04/02, is acknowledged.

Applicants' arguments filed in Paper No. 18 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification/Informalities

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method for Producing L-Amino Acids using a *Corynebacterium glutamicum* with a Disrupted *pgi* Gene". See MPEP § 606.01.

Claim Objections

2. Claims 1 and 6 objected to because of the recitation of "pgi". Abbreviations, unless otherwise obvious should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that applicants replace the first occurrence of "pgi" at line 4 of claim 1 with, for example, "phosphoglucose isomerase (pgi)". Appropriate correction is required. It is noted that claims 8 and 18-21 have not been objected to because claim 7 identifies the term for which the abbreviation "pgi" is used.

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3. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. It is clear from lines 3 and 4 of claim 1 (from which claim 7 depends) that the *C. glutamicum* has a disrupted *pgi* gene. Therefore, claim 7 does not further limit claim 1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

4. Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. By definition, a *pgi* that is disrupted is necessarily a mutant *pgi* gene. Therefore, claim 20 does not further limit claim 18. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8 and 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 8 and 21 are incomplete as carrying out steps (a) and (b) do not necessarily result in disruption of a *pgi* gene. One of skill in the art would recognize that by inserting an internal region of a gene by homologous recombination would recreate the original gene. It is noted that the specification discloses at lines 4 and 5 of page 30 that the vector into which the internal fragment was cloned is a suicide vector. It is suggested that applicants clarify the meaning of the claims.

b. Claims 8 and 21 recite the limitation "said resulting vector from step (a)" in line 4. There is insufficient antecedent basis for this limitation in the claims. In order to correct antecedent basis, it is suggested that, for example, applicants insert the term "into a vector" following

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"subcloning an internal region of a *pgi* gene" or replace the term "inserting said resulting vector from step (a)" with, for example, "inserting said internal region of a *pgi* gene from step (a)".

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 6-8, and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing L-lysine, L-threonine, or L-isoleucine using an altered *C. glutamicum* cell with a disrupted *pgi* gene with yields about 25 % greater than a *C. glutamicum* cell having a non-disrupted *pgi* gene, does not reasonably provide enablement for a method of producing L-lysine, L-threonine, or L-isoleucine by culturing an altered *C. glutamicum* cell having a disrupted *pgi* gene with yields greater than about 25 % relative to a *C. glutamicum* cell having a non-disrupted *pgi* gene, or a method of producing L-lysine, L-threonine, or L-isoleucine by culturing an altered *C. glutamicum* cell having a decreased amount of 6-phosphoglucose isomerase enzyme activity and a disrupted *pgi* gene with yields greater than about 25 % relative to a *C. glutamicum* cell having a non-disrupted *pgi* gene.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Undue experimentation would be required to make the invention broadly encompassed by the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

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Claims 1 (claims 7 and 8 dependent therefrom), 6, 18 (claims 20 and 21 dependent therefrom), and 19 are so broad as to encompass a method for producing L-lysine, L-threonine, or L-isoleucine with relative yields that are not commensurate with the disclosure provided by the specification as described above. The use of *C. glutamicum* bacteria for the production of amino acids is well known in the art. Furthermore, methods of increasing the amino acid yields of a *C. glutamicum* cell by genetic modification are also well known in the art. However, the specification provides guidance *only* for generating a *C. glutamicum* with a disrupted *pgi* gene having relative increased yields of L-lysine of about 25 % (see particularly Table A at page 30 of the instant specification). There is no evidence in the specification or the prior art that disruption of a *C. glutamicum* *pgi* gene will result in the recited levels of amino acids. The specification provides no guidance or working examples for a method of producing L-lysine, L-threonine, or L-isoleucine with unlimited increased yields or increased yields of up to 100 % as encompassed by the claims. It is highly unlikely that disruptions of the same gene would result in substantially different yields. Therefore, it is highly unlikely that a skilled artisan, provided the disclosed method, could produce unlimited increased yields of L-lysine, L-threonine, or L-isoleucine or increased yields as high as 100 % relative to an unmodified *C. glutamicum* cell.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

It is noted that a scope of enablement rejection under 35 USC 112, first paragraph, has been raised in a previous Office action (see Paper No. 7) and maintained in a subsequent Office action (see Paper No. 11). The scope of enablement rejection of claims 1 and 6 was withdrawn and maintained for claims 7 and 18-20. However, while the rejection of claims 1 and 6 has been withdrawn, upon reconsideration the examiner has re-instated the rejection. The examiner has re-instated the rejection

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because the claimed yields of amino acids are not commensurate with the enablement provided by the specification as described above.

Claim Rejections - 35 USC § 103

7. Rejection of claims 1, 6, 7, and 18-20 under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. (Appl Environ Microbiol 57:2995-9) in view of Ishino et al. (J Gen Appl Microbiol 37:157-165), Voet et al. (Biochemistry 2nd Edition, Wiley and Sons, 1995, NY), and Sahm et al. (Ann NY Acad Sci 782:25-39), is withdrawn for the reasons described below. The prior art clearly suggests that a *C. glutamicum* cell with a disrupted *pgi* gene will result in increased yields of tryptophan produced by said *C. glutamicum*. For example, Liao et al. (US Patent 5, teach a method of producing tryptophan using a *C. glutamicum* cell having a deletion of a *pgi* gene (column 20, line 6). Furthermore, the prior art suggests that disruption of an *E. coli* *pgi* gene may result in an increased level of glutamate (see page 2998, bottom right of Mascarenhas et al.). However, the examiner can find no teaching in the prior art of record to suggest that increased levels of tryptophan or glutamate produced by *C. glutamicum* cell correlate with an increased production of L-lysine, L-threonine, or L-isoleucine. Thus, there is no clear expectation of success that the teachings of Liao or Mascarenhas et al. enable a method of producing increased yields of L-lysine, L-threonine, or L-isoleucine using a *C. glutamicum* with a disrupted *pgi* gene relative to a *C. glutamicum* cell with a non-disrupted *pgi* gene.

8. Rejection of claims 8 and 21 under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. in view of Ishino et al., Voet et al., and Sahm et al. as applied to claims 1, 6, 7, and 18-20 and further in view of Fitzpatrick et al. (Appl Microbiol Biotechnol 42:575-580) is withdrawn. The reference of Fitzpatrick et al. does not correct the deficiencies of the references of Mascarenhas et al., Ishino et al., Voet et al., and Sahm et al., nor does the reference provide any suggestion that increased levels of tryptophan or glutamate produced by *C. glutamicum* cell correlate with an increased production of L-lysine, L-threonine, or L-isoleucine. Therefore, there is no clear expectation of success that the teachings of the cited prior art references enable the claimed method.


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Conclusion

9. All claims are rejected.
10. No claim is in condition for allowance.
11. Claims 1, 6-8, and 18-21 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, first paragraph, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


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